Original Article

Evaluation of Initial Respiratory Support Strategies in VLBW Neonates with RDS

Seyyed Abolfazl Afjeh MD•[1,2], Mohammad Kazem Sabzehei MD[3], Maryam Khoshnood Shariati MD[2], Ahmad Reza Shamshiri MD[4], Fatemeh Esmaili BSc[2]

Abstract

Background: Non-invasive ventilation (NIV) has brought about a significant change in care and treatment of respiratory distress syndrome (RDS) in very low birth weight (VLBW) neonates. The present study was designed and conducted to evaluate different strategies of initial respiratory support (IRS) in VLBW neonates hospitalized in the neonatal intensive care unit (NICU).

Methods: This prospective study was conducted over three years (March 21, 2011 to March 20, 2014). Each eligible VLBW baby with RDS diagnosis received a specific IRS, including room air (RA), oxygen therapy (O2 RX), n.CPAP, NIPPV, MV ± SURF, based on clinical evaluation; then, the next strategies were selected based on the disease progression. Obtained data was entered in SPSS and the groups were compared for disease consequences or death. Then, contributing factors to the failure of NIV strategies, and the need for endotracheal mechanical ventilation (eMV) were determined.

Results: In total, 499 neonates were included in the study. The mean birth weight was 1,125 ± 254 g and the gestational age was 29.2 ± 2.5 weeks. The IRS included: RA = 43, O2.RX = 60, n.CPAP/NIPPV = 219, INSURE = 83 and MV ± SURF = 177. In terms of the need for IRS upgrading during hospitalization, neonates not on mechanical ventilation (64.5%) were divided into three groups. In 45.3% of cases, the IRS did not change (Never upgrading); in 24.5% of cases, the level of IRS increased but there was no need for eMV in the first three days of life (Specific); in 24.8% of cases, there was need for eMV within the first three days of life (Absolute) and during hospitalization (after the first three days of life) 5.3% of cases were in need of eMV (General).

In terms of correlation between the effective variables in IRS upgrading, univariable analyses showed that low gestational age, low birth weight, multiple pregnancy, maternal disease, low one-minute Apgar score, and need for surfactant therapy had significant correlation, and multivariable analysis showed that low gestational age, low birth weight and maternal disease were risk factors independently correlated to IRS upgrading, CLD and death.

Conclusion: Early use of NIV in preterm neonates with mild to moderate respiratory distress and spontaneous breathing significantly reduced the need for intubation, surfactant, mechanical ventilation and thereby pulmonary and non-pulmonary complications and neonatal mortality.

Keywords: Respiratory distress syndrome, respiratory support strategies, risk factors, VLBW neonate

Cite this article as: Afjeh SA, Sabzehei MK, Khoshnood Shariati M, Shamshiri AR, Esmaili F. Evaluation of initial respiratory support strategies in VLBW neonates with RDS. *Arch Iran Med*. 2017**; 20(3):** 158 – 164.

Introduction

RDS is the most prevalent cause of VLBW neonate hospitalization in the NICU, and the most important cause of mortality among these neonates. The prevalence of RDS has been reported up to 90%, based on the gestational age; this rate was 71.8% in our research site.[1]

The eMV and surfactant (SURF) administration has become the standard care (STD-Care) since 1990. However, following the report by Northway (1967) about the incidence of broncho-pulmonary dysplasia (BPD) following eMV, Avery (1986) showed that early use of nCPAP, administered in Colombia University, significantly reduced the incidence of BPD, as compared to other centers where eMV was used.[2]

As a result of scientific and technological advance, studies have shown that the severity of RDS is directly correlated with functional residual capacity (FRC), which can be achieved by early use of nCPAP instead of SURF. Therefore, a trend was initiated towards comparative studies between nCPAP and eMV: in 1999, Linder showed that administration of nCPAP reduced the need for intubation in 25% of patients with extremely low birth weight (ELBW). In addition, Van Marter (2001) reported BPD reduction following nCPAP.[3]

Verder (1992) introduced INSURE (Intubation, Surfactant, Extubation) by reporting the added benefit of combining SURF with nCPAP,[4] Later in 2007, Kugelman introduced nasal intermittent positive pressure ventilation (NIPPV) as nCPAP substitute for initial respiratory support.[5]

Three large studies in 2008 (COIN)[6], 2010 (SUPPORT)[7] and 2011 (VON-DRM)[8], and comparison of nCPAP ± INSURE *vs.* eMV + SURF did not show a significant difference in rates of mortality and BPD among the investigated neonates.

Accordingly, non-invasive methods (nCPAP, NIPPV, and INSURE) have been shown to be effective in reducing the use

Authors' affiliations: [1]Neonatal Health Research Center (NHRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2]Mehdieh Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Hamedan University of Medical Sciences, Hamedan, Iran, [4]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

•Corresponding author and reprints: Seyyed Abolfazl Afjeh MD, Newborn Service, Mahdieh Medical Center, Shoosh Square, Shahrezad Street, Tehran, Iran. Tel: +98-21-55266282, E-mail: a_afjeh@sbmu.ac.ir.

Accepted for publication: 25 January 2017

of eMV and its complications, which can be effective in the prevention of BPD.[9] In addition, European consensus (2016) and the AAP (2014) have recommended using non-invasive methods as IRS.[10,11]

This study set out to evaluate different strategies of IRS (from the birth) in VLBW neonates with mild, moderate, and severe RDS to evaluate the success or failure rate and incidence of complications from each strategy in the first three days of life and later during the course of hospital stay.

Materials and Methods

This three-year prospective study (March 21, 2011 to March 20, 2014) was conducted for VLBW neonates hospitalized in the NICU of Mahdieh Hospital with RDS diagnosis; out-born neonates were included if admitted within the first 24 hours of life, based on the IRS. The exclusion criteria were neonates with major anomalies incompatible with life, known syndromes, and chromosome disorders.

Mahdieh Hospital, affiliated to Shahid Beheshti University of Medical Sciences (SBUMS), is a level III perinatal center in Tehran, capital of Iran. It has 39 NICU beds and a rate of almost 5,000 live births per year. Maternal and neonatal demographic information were gathered and recorded in specific forms (Tables 1 and 2)

The care procedure for the VLBW neonates in this center included the presence of skilled delivery room staff, performing CPR if needed, and initiation of respiratory support at birth.[10,11]

The neonates were divided into three groups at birth based on the severity of respiratory distress and IRS as follow:[3,6–8]

I. Group I (RA/O2.RX): Active neonates with spontaneous breathing, mild distress, and RDS score < 3, in room air or FIO_2< 30% during oxygen administration.

II. Group II (nCPAP/NIPPV): neonates with moderate respiratory distress (3 ≤ RDS score ≤ 6), who received respiratory support by the Neo-Puff (T. Piece Resuscitator), from birth up to transfer to the NICU.

III. Group III (MV ± SURF): neonates with breathlessness, cyanosis, and/or severe respiratory distress (RDS score > 6), who needed eMV at birth in the delivery room, using the Neo-Puff and decision to use SURF was made in the first two hours of life following transfer to the NICU.

Neonates in the first and second groups were placed either in the "Success: Never Upgrading" group, if there was no need for IRS improvement, or in the "Failure: Upgrading" group in case of IRS failure. Upgrading in the first three days of life without need for intubation and mechanical ventilation was categorized as "Specific"; while upgrading in the first three days of life with need for intubation and mechanical ventilation was categorized as "Absolute" and after the third day of life until discharge (or death) with need for intubation and mechanical ventilation was categorized as "General."

After all neonates were transferred to the NICU, the IRS: oxygen therapy via blender ± oxyhood, nCPAP/NIPPV was continued with single or bi-nasal prong (SNP/BNP) by Bubble CPAP (B.CPAP), Infant flow driver (IFD), or Ventilator CPAP with following Setup: FiO_2 adjusted to $SPaO_2$ = 89% – 92%, PEEP = 4 – 6 cmH_2O, and with NIPPV by ventilator (preferably in n-SIMV mode): FiO_2 = adjusted to $SpaO_2$ = 89% – 92%, PIP = 10 – 25 cmH_2O, RR = 10 – 50/min, IT = 0.3 – 0.5 sec.[12]

Monitoring of the neonates continued based on clinical (respiratory distress), chest X-ray, and ABG. In case of developing failure criteria in group I & II: persistent respiratory distress, FiO_2 > 40%, PH < 7.25, $PaCO_2$ > 60mmHg, the need for PEEP > 6 cmH_2O to have $SpaO_2$ = 89% – 92%, frequent apnea > 3 times/hr (longer than 20 seconds with HR < 100/min and no response to caffeine, or need for PPV using the Bag & Mask), IRS upgrading was done. Although this was normally made stepwise (RA to O2.RX, O2.RX to n.CPAP, n.CPAP to NIPPV, NIPPV to INSURE, INSURE to MV± SURF), there were some exceptions.[2]

Diagnosis of CLD is based on need for oxygen at 36 weeks postmenstrual age (PMA), Bell Staging Criteria for NEC, international classification for ROP, and intraventricular hemorrhage (IVH), according to Papille classification.[1]

This study was approved by the Ethical Committee of the SBUMS; in addition, informed consent was obtained from parents.

Statistical Methods

Categorical variables were reported as numbers as well as percentages, and quantitative variables were summarized as mean and standard deviation (SD). To evaluate the relationship between different IRS methods (three categories) with some predictors or outcome variables, multinomial regression analysis was performed. In addition, in case of different types of IRS upgrading (three categories) and their relationship with other variables, simple and multiple multinomial regression were used. All *P*-values less than 0.05 were considered as statistically significant.

Results

Of 13,412 live births during the three-year period (March 21, 2011 to March 20, 2014) in this center, 405 inborn and 94 outborn neonates, in total 499 VLBW neonates with RDS were enrolled. The mean gestational age, mean birth weight, multiple pregnancy, C-section, and male gender were 29.2 ± 2.5 weeks, 1,125 ± 254 g, 217 (43.5%), 411 (82.4%), and 268 (53.7%), respectively. In addition, 23.8% of mothers had underlying diseases including infertility (20%), preeclampsia (18.4%), premature rupture of membranes (8.2%), diabetes (6.2%), Placenta abruption (7.6%) and chorioamnionitis (2.4%).

The initial respiratory support for these 499 neonates included: RA/O2.RX: 103(20.6%), n.CPAP/NIPPV: 219 (43.9%), eMV ± SURF: 177 (35.5%). The general characteristics of neonates are provided in Table 1.

Respiratory and non-respiratory complications from birth to discharge (or death) are presented in Table 2. The provided information demonstrates an increase in pulmonary complications (pneumothorax, pulmonary hemorrhage), non-pulmonary complications (sepsis, PDA, IVH, NEC, and ROP) and neonatal death, following the use of eMV compare to the other two groups (Table 3).

During the hospital course, of 322 neonates (except 177 with MV ± SURF), the non-invasive initial respiratory support was successful in 147 (41.7%) neonates (never upgrading), but failure (Upgrading) was observed as: Absolute in 80 (23.7%), Specific in 75 (21.3%) and General in 20 (5.7%) neonates, Therefore, the use of non-invasive IRS decreased the need for eMV in 242 (75.1%) neonates in the first three days of life and in 222 (never upgrading: 147, specific: 75) neonates (68.9%) during hospital course (Table 4).

Table 1. Neonates' characteristics

Characteristics	Room air / Oxygen (N = 103)	n.CPAP / NIPPV (N = 219)	MV ± surfactant (N = 177)
Birth.weight.gr	1266.84 ± 187.07	1140.78 ± 253.63	1024.8 ± 247.54
>= 1000 gm.	94 (27.4%)	155 (45.2%)	94 (27.4%)
< 1000 gm.	9 (5.8%)	64 (41%)	83 (53.2%)
Gestational. Age. (Mean ± SD)	31.48 ± 2.32	29.33 ± 2.08	27.94 ± 2.18
> 28w	88 (29.7%)	142 (48%)	66 (22.3%)
<= 28w	15 (7.4%)	77 (37.9%)	111 (54.7%)
Sex			
Female	54 (23.4%)	99 (42.9%)	78 (33.8%)
Male	49 (18.3%)	120 (44.8%)	99 (36.9%)
Multiple Pregnancy	46 (21.19%)	99 (45.62%)	72 (33.17%)
Maternal. Dis	39 (17.80%)	101 (46.11%)	79 (36.07%)
PROM+ Chorioamnionitis	11 (20.75%)	17 (32.07%)	25 (47.16%)
ART	16 (16%)	52 (52%)	32 (32%)
Antenatal steroid	103 (20.6%)	219 (43.9%)	177 (35.5%)
Birth. Place. Inborn	82 (19.3%)	187 (44%)	156 (36.7%)
Delivery. type (C/S)	86 (20.9%)	189 (46%)	136 (33.1%)
APGAR.1"(Mean ± SD)	7.97 ± 1.6	7.41 ± 1.69	5.76 ± 2.28
<= 6	16 (9%)	59 (33.3%)	102 (57.6%)
APGAR.5"(Mean±SD)	9.31 ± 1.03	8.85 ± 1.31	7.41 ± 1.91
<= 6	0 (0%)	10 (18.5%)	44 (81.5%)

NIPPV: Non Invasive Positive Pressure Ventilation; n.CPAP: Nasal Continuous Positive Airway Pressure; MV: Mechanical Ventilation; Maternal disease: Diabetes, Placenta Previa, Bleeding, Pre-eclampsia and others; PROM: Premature Rupture of Membrane; ART: Artificial Reproductive Technology.

Table 2. Neonates Complications

Characteristics	Room air / Oxygen (N = 103)	n.CPAP / NIPPV (N = 219)	MV ± Surfactant (N = 177)
CPR			
O2	87 (84.5%)	206 (94.1%)	177 (100%)
PPV	18 (17.5%)	102 (46.6%)	135 (76.3%)
Intubation	2 (1.9%)	16 (7.3%)	82 (46.3%)
Chest compression	0 (0%)	1 (0.5%)	15 (8.5%)
Drugs	0 (0%)	0 (0%)	8 (4.5%)
Apnea	16 (15.5%)	114 (52.1%)	73 (41.2%)
Pneumothorax	1 (1%)	20 (9.1%)	31 (17.5%)
Pulmonary Hemorrhage	5 (4.9%)	20 (9.1%)	28 (15.8%)
IVH >G2	0 (0%)	7 (3.19%)	11 (6.21%)
Sepsis (+/- meningitis)	8 (7.8%)	76 (34.7%)	80 (45.2%)
Sepsis			
Clinical	2 (1.9%)	4 (1.8%)	15 (8.5%)
Probable	4 (3.9%)	50 (22.8%)	50 (28.2%)
Definite	2 (1.9%)	22 (10%)	15 (8.5%)
PDA	29 (28.2%)	114 (52.1%)	98 (55.4%)
NEC (Stage >= 2)	1 (1%)	3 (1.4%)	6 (3.4%)
ROP(Stage >= 2)	8 (7.8%)	42 (19.2%)	27 (15.3%)
CLD	1 (1%)	5 (2.3%)	17 (9.6%)
Hospital Course (day) (Mean ± SD)	26.14 ± 14.64	33.87 ± 20.52	27.91 ± 27.91
Outcome			
Survive	97 (94.2%)	177 (80.8%)	84 (47.5%)
Cause of death			
Respiratory	4 (66.7%)	29 (69%)	68 (73.1%)
Non-Respiratory	2 (33.3%)	13 (30.95%)	25 (26.88%)

CPR: Cardio Pulmonary Resuscitation; IVH: Intra Ventricular Hemorrhage; NEC: Necrotizing Enterocolitis; ROP: Retinopathy of Prematurity; PDA: Patent Ductus Arteriosus; CLD: Chronic Lung Disease.

Table 3. IRS and outcomes relationship (Multinominal Regression Analysis)

Complication	"n.CPAP / NIPPV" *vs.* "Room air / Oxygen"			"MV +/– surfactant" *vs.* "Room air / Oxygen"			"MV +/– Surfactant" *vs.* "n.CPAP / NIPPV"		
	OR	95%CI of OR	*P*–Value	OR	95%CI of OR	*P*–Value	OR	95%CI of OR	*P*–Value
Apnea	5.9	3.25–10.71	< 0.001	3.82	2.07–7.03	< 0.001	0.65	0.43–0.96	0.03
Pneumothorax	10.25	1.36–77.47	0.02	21.66	2.91–161.21	0.003	2.11	1.16–3.85	0.01
Pulmonary Hemorrhage	1.97	0.72–5.41	0.19	3.68	1.38–9.86	0.009	1.87	1.01–3.45	0.04
PDA	2.77	1.67–4.59	< 0.001	3.17	1.88–5.33	< 0.001	1.14	0.77–1.7	0.51
Sepsis (+/– meningitis)	6.31	2.91–13.68	< 0.001	9.79	4.49–21.36	< 0.001	1.55	1.03–2.33	0.03
IVH (Grade > II)*	4.63	0.68–infinity	0.13	9.44	1.51–infinity	0.01	2.00	0.69–6.24	0.23
NEC (stage ≥ II)	1.42	0.15–13.79	0.76	3.58	0.42–30.15	0.24	2.53	0.62–10.25	0.19
ROP (stage ≥ II)	2.82	1.27–6.25	0.01	2.14	0.93–4.9	0.07	0.76	0.45–1.29	0.31
CLD	2.38	0.27–20.66	0.43	10.84	1.42–82.68	0.02	4.55	1.64–12.59	0.004
Mortality	3.84	1.57–9.35	0.003	17.9	7.46–42.97	< 0.001	4.67	2.98–7.3	< 0.001
*Analyzed with exact logistic regression by STATA software; IRS: Initial Respiratory Support									

Table 4. IRS and follow up during hospital course

Non Invasive	Never Upgrading	Upgrading		
		Specific (< 3 day; no eMV)	Absolute (< 3 day+eMV)	General (> 3 day+eMV)
Room Air (n = 43)	39 (90.6%)	1	2 (4.6%)	1
O2.RX (n = 60)	41 (68.3%)	12 (INSURE = 4)	2 (3.3%)	5
n.CPAP (n = 56)	19 (33.9%)	21 (INSURE = 12)	11 (19.6%) INSURE = 3	5
NIPPV (n = 163)	48 (29.4٪)	41 (INSURE = 41)	65 (39.9%) INSURE = 21	9
Invasive	Never eMV.off	eMV < 3d (Early Extubation)	eMV > 3 d	---
MV ± SURF (n = 177)	56 (31.4%) Expire	113 (63.8%) n.CPAP/NIPPV (INSURE = 2)	45 (25.4%), 4–45 d	---
eMV: Endotracheal Mechanical Ventilation				

Table 5. Simple Multinominal Regression Analysis

Characteristics	Specific *vs.* Never upgraded			Absolute *vs.* Never upgraded		
	OR	95%CI	*P*–Value	OR	95%CI	*P*–Value
Sex						
Female	1.00	---	---	1.00	---	---
Male	1.47	0.85–2.56	0.17	1.29	0.75–2.23	0.36
Gestational age						
> 28 w	1.00	---	---	1.00	---	---
<= 28 w	2.68	1.43–4.99	0.002	2.77	1.49–5.15	0.001
Birth weight						
>= 1000 gm	1.00	---	---	1.00	---	---
< 1000 gm	1.44	0.68–3.05	0.34	4.69	2.43–9.05	< 0.001
Maternal disease						
Yes	0.97	0.54–1.74	0.92	2.19	1.25–3.82	0.006
No	1.00	---	---	1.00	---	---
PROM and/or Chorioamnionitis						
Yes	0.23	0.05–1.02	0.05	0.58	0.2–1.67	0.31
No	1.00	---	---	1.00	---	---
Plurality						
Single	1.00	---	---	1.00	---	---
Multiple	0.81	0.47–1.41	0.46	0.55	0.32–0.97	0.04
Delivery type						
NVD	1.00	---	---	1.00	---	---
C/S	0.42	0.2–0.89	0.02	0.65	0.29–1.46	0.30
APGAR.1						
> 6	1.00	---	---	1.00	---	---
<= 6	1.33	0.67–2.64	0.42	2.20	1.16–4.17	0.02
APGAR.5						
> 6	1.00	---	---	1.00	---	---
<= 6	0.61	0.06–5.97	0.67	3.18	0.74–13.66	0.12
Surfactant						
Yes	186.55	42.48–819.21	< 0.001	312.00	69.33–1404.17	< 0.001
No	1.00	---	---	1.00	---	---

Table 6. Multiple Multinominal Regression Analysis

Characteristics	Specific *vs.* Never upgraded			Absolute *vs.* Never upgraded		
	OR	95%CI	*P*-Value	OR	95%CI	*P*-Value
Gestational age						
> 28 w	1.00	---	---	1.00	---	---
<= 28 w	2.73	1.4–5.31	0.003	2.00	0.99–4.03	0.052
Birth weight						
>= 1000 gm	1.00	---	---	1.00	---	---
< 1000 gm	0.96	0.42–2.17	0.92	3.34	1.64–6.82	< 0.001
Maternal disease						
No	1.00	---	---	1.00	---	---
Yes	1.07	0.59–1.95	0.82	2.13	1.18–3.85	0.01

The INSURE method was applied for 83 neonates after failure of O2.RX (n = 4), n.CPAP (n = 15), NIPPV (n = 62), and to two neonates after extubation from eMV. The rates of INSURE success and failure were 71.1% (59 neonates) and 28.9% (24 neonates), respectively (Table 4).

Of 177 neonates with eMV from birth, 113 (63.8%) neonates were extubed in the first three days of life and 45 of them remained on eMV for more than three days (25 neonates for 4 – 14 days; 19 for 2 – 4 weeks, and one for 45 days). Finally, 93 (52.5%) neonates died (56 under eMV, of which 46 deaths occurred in the first three days of life), and 84 (47.5%) neonates survived (Tablel 4).

With respect to the correlation of risk factors in non-invasive IRS failure, univariable analysis revealed gestational age ≤ 28 weeks, birth weight < 1,000 g, multiple pregnancy, maternal diseases, one-minute APGAR ≤ 6, and need for SURF as independent risk factors; multivariable analysis indicated gestational age ≤ 28 weeks, birth weight < 1,000 g, and maternal diseases as independent risk factors contributing to failure and IRS upgrading (Specific and Absolute versus Never Upgrading) (Tables 5 and 6).

Discussion

IRS in VLBW neonates with RDS is a real challenge in the present decade.[13] Although MV ± SURF has been presented as the STD-care since 1990, the development of complications such as Ventilator Associated Pneumonia (VAP), Late Onset Sepsis (LOS), Broncho Pulmonary Dysplasia (BPD), and Neuro Developmental Delay (NDD)[9] followed by results from various

studies that showed many VLBW (even ELBW) neonates have spontaneous breathing at birth, some of them with nCPAP (even without the administration of surfactant) do not need eMV,[7] and there is no significant difference with the STD-care *vs*. NIV group in terms of significant complications, especially BPD/death.[14]

In this prospective study, 499 VLBW neonates received IRS at birth by considering the risk factors[15] and clinical evaluation, but in the COIN,[6] SUPPORT[7] and VON_DRM[8] studies, the neonates were enrolled 5-minute after birth, before labor, and 5 – 15 minutes after birth, respectively.

Our study showed that only 35.5% of the VLBW neonates required MV ± SURF at birth, 43.9% were managed with nCPAP/NIPPV and 20.6% with RA/O2.RX as IRS (Table 1).

In group I (RA/O2.RX), did they require eMV or nCPAP at birth because of gestational age, birth weight, risk of apnea, and probably worsen RDS? Alternatively, are they in need of prophylactic nCPAP, which is not recommended?[16]

Therefore, we continued IRS and careful monitoring during hospital course, specifically in the first three days of life, and the failure rate was 22.3% (Tables 3 – 6).

Unfortunately, previous studies have not addressed IRS in this group of neonates, and thus a comparative study such as Prophylactic *vs*. Rescue n.CPAP may be helpful in this group of neonates.

In group II (nCPAP/NIPPV), the difference in number of neonates on NIPPV versus nCPAP was due to the limitations of CPAP (B.CPAP, IFD, …) and using current equipment (ventilators), mostly for NIPPV.

Although the majority of studies recommend the early use of nCPAP at birth,[10,11,13,17] the introduction of NIPPV into NIV group in recent years,[12,18,19] provision of physiological principles,[12,20] priority of NIPPV over nCPAP,[5] higher success of NIPPV *vs*. nCPAP[21] and recommendation for use of NIPPV as a bridge in nCPAP failure (before INSURE), and after INSURE failure (before eMV),[22,23] bring up the question whether or not the NIPPV is superior over nCPAP when ventilator is in use. It is worthy to indicate the reported role of synchronization and its implementation (S.NIPPV) in the success of NIPPV.[12,24]

In our study, only 11 (19.6%) out of 56 (26.6%) neonates who were on nCPAP as IRS needed eMV in the first three days of life (CPAP Success: 80.4% *vs*. failure 19.6%). This finding is consistent with the findings of Ammari[25] (76% success in neonates with birth weight < 1,250 g), Fuchs[26] (49% success in preterm neonates with gestational age < 29 weeks), and Dragaville (78% success in neonates with gestational age ≤ 32 weeks).[27]

In terms of risk factors for CPAP failure, our study incriminated low gestational age, low birth weight, and maternal diseases. Ammari reported the incredible low birth weight (ILBW ≤ 750 g), gestational age less than 26 weeks, severity of RDS (severe RDS in the first chest X-ray), and need for PPV at birth,[25] Fuchs reported positive medical history and deteriorated ABG,[26] Dragaville reported low gestational age, persistent RDS, and the need for $FiO_2 \geq 30\%$ at the early hours of life,[27] Pillai reported gestational age less than 28 weeks, PROM, and CPAP pressure × FiO_2 > 1.28 at initiation to provide saturation 88% – 93%,[28] as independent risk factors for CPAP failure. These studies are consistent with ours with regard to the role of birth weight and gestational age.

In this group, 163 neonates (74.4%) received NIPPV, of which 65 neonates (39.9%) received eMV in the first three days of life (success 60.1% vs NIPPV failure: 35.9%). The application of NIPPV (versus nCPAP) as IRS (primary mode) dates back to 2004 – 2012 in six studies conducted on 574 neonates; the results of those studies showed that use of NIPPV reduced the rate of intubation, BPD in VLBW neonates, apnea, $Paco_2$, duration of respiratory support, etc.[12] Manzer, et al. reported the achievement of NIPPV in reducing the need for intubation and mechanical ventilation in 81% of cases.[29] This achievement was reported as 75% by Kugeman, et al.[5]

In this group, use of nCPAP/NIPPV *vs*. MV ± SURF, reduced the frequency of pneumothorax, pulmonary hemorrhage, sepsis, BPD and neonatal death (Table 3).

To prevent nCPAP/NIPPV failure or when failure criteria appear, and to benefit from surfactant advantages, the INSURE method was introduced by Verder[4] in 1992. Based on the age of INSURE, it was categorized as Early (from DR up to 2 hours) or Late (after 2 hours).

There are limited comparative studies between Early.INSURE *vs*. Early.n.CPAP & STD Care and Late INSURE *vs*. nCPAP & STD Care, which have shown that INSURE success reduced the need for eMV.[13]

In this study, 83 newborns received INSURE (Table 4), early INSURE in 51.8% and INSURE Success (reducing eMV in the first three days of life) was 71.1%. This rate has been reported between 50% – 100% by other studies.[13]

In group III (MV ± SURF), although eMV is considered as the mainstay of RDS therapy in VLBW, provision of alternative therapy (nCPAP/NIPPV) for a certain group of neonates (specifically those with GA > 28 w and Bwt > 1,000 g), resulted in prevention or reduction of eMV duration.[9]

The results of seven studies (COIN, CNRN, SUPPORT, CURPAP, DRM, AMV, Take Care) have shown that between 31% – 83% of neonates needed eMV.[17] In addition, Walsh reported the use of eMV for 85% and 95% of surviving ELBW neonates on the first day of life and during hospital course, respectively;[9] however in our study, in addition to the 177 neonates who received mechanical ventilation at birth, 80 neonates (24.3%) in the first three days of life and 20 neonates (6.2%) after the third day of life (group I, II), in total 277 (55.5%) neonates, received eMV which is acceptable (Table 4).

The most important concern regarding mechanical ventilation is the incidence of BPD/death; our study also showed an increased risk of BPD/death, and neonatal death in GIII *vs*. GI and GII (Table 3). Therefore, it seems that there is need for new strategies on neonatal respiratory care rather than STD-care.

With regard to the correlation of other complications with respiratory strategy in our study, it has been shown that the frequency of pulmonary damage from eMV (PAL, Pulmonary Hemorrhage), as well as non-pulmonary complications (PDA, IVH, NEC, ROP, and Sepsis) is greater when eMV is applied (Tables 2 and 3). This finding is consistent with the findings of Stevens TP[30] and Agular[31] showing higher respiratory complications in the eMV group. It is also consistent with Ammari's findings showing that the incidence of complications (even in the CPAP Failure group) was significantly lower compared to neonates receiving eMV at birth.[25]

With respect to the administration of surfactant,[32,33] 166 and 83 neonates in our study received surfactant via eMV and INSURE, respectively. In total, 249 neonates (49.8%) received SURF (Table 4). In Ammari's study, 53% in the eMV group and 50% in the NIV Failure Group received surfactant, indicating the reduced

use of SURF when NIV is applied.[25]

The limitations of our study include limited equipment, especially for nCPAP (B.CPAP, IFD, …) and limited ratio of nurse : neonate (1: 4) which affects quality of care.

In conclusion, this study showed that provision of IRS based on clinical evaluation at birth, non-invasively for stable and moderately ill infants and invasively for critically ill neonates, reduced the use of eMV and SURF therapy, pulmonary and non-pulmonary complications, as well as neonatal death.

Although we did not aim to compare different non-invasive IRS technique (nCPAP/NIPPV) with each other and with eMV, we look forward to conducting such comparative studies in the not too distant future.

Acknowledgments

We hereby thank the Neonatal Health Research Center (NHRC), SBUMC, for its support and cooperation in the conduction of this study, as well as all colleagues (physicians, nurses, and staff) in the Neonatal Unit of Mahdieh Hospital.

Reference

1. Afjeh SA, Sabzehei MK, Fallahi M, Esmaili F. Outcome of very low birth weight infants over 3 years report from an Iranian center. *Iran J Pediatr*. 2013; 23 (5): 579 – 587.
2. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics*. 1987; 79(1): 26 – 30.
3. Robert H, Roger F. Initial respiratory support of preterm infants. *Clin Perinatal*. 2012; 39: 459 – 481.
4. Verder H, Agertoft L, Albertsen P, Christensen NC, Curstedt T, Ebbesen F, et al. Surfactant treatment of newborn infants with respiratory distress syndrome primatory treated with nasal continuous positive air way pressure. A pilot study. *Ugeskr Laeger*. 1992; 154(31): 2136 – 2139. [in Danish]
5. Kugelman A, Fefrkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: A randomized, controlled, prospective study. *J Pediatr*. 2007; 150(5): 521 – 526.
6. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. COIN trial investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008; 358(7): 700 – 708.
7. Finer NN, Carlo WA, Walsh MC, Support study group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010; 362(21): 1970 – 1979.
8. Duun MS, Kaempf J, de Klerk A, Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics*. 2011; 128(5): e1069 – e1076.
9. Matrin K, Guilhermee SA. Mechanical ventilation and bronchopulmonary dysplasia. *Clin Perinatal*. 42(2015): 781– 796.
10. David GS, Virgilio C, Gorm G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome–2016 update. *Neonatology*. 2017; 111: 107 – 125.
11. American Academy of Pediatrics. Committee on Fetus and Newborn. respiratory support in preterm infants at birth. *Pediatrics*. 2014; 133: 171.
12. Vineet B. Noninvasive respiratory support in the preterm infants. *Clin Perinatal*. 2012; 39: 497 – 511.
13. Finer N. To intubate or not-that is the question: Continuous positive airway pressure versus surfactant and extremely low birth weight infants. *Fetal Neonatal Ed*. 2006; 91: F392 – F394.
14. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in Preterm Infants at Birth: Systematic review and meta-analysis. *BMJ*. 2013; 347(347): f5980.
15. Arun K, Nandeesh R, Thomas G. Neonatal Respiratory Distress. *Pediatr Clin N Am*. 2015; 2(62): 453 – 469.
16. Polin R A, Rakesh S. Continuous positive airway pressure: Old questions and new controversies. *Neonatal Perinatal Medicine*. 2008; 1: 1 – 10.
17. Hendrik S, Buhrer F, Buhrer CH. Avoiding endotracheal ventilation to prevent broncho pulmonary dysplasia: A meta-analysis. *Pediatrics*. 2013; 132; e1351.
18. James J, Polin RA. Noninvasive respiratory support. *Pediatrics*. 2016; 137(1): e20153758.
19. 19-Jensen EA, Kirpalani H. Non-invasive respiratory support. *Seminars in Fetal & Neonatal Medicine*. 2016; 21(3): 133 – 134.
20. Stamatia A, Howard BP. Physiology of non-invasive respiratory support. *Seminars in Fetal & Neonatal Medicine*. 2016; 21: 174 – 180.
21. Bisceglia M, Belcastro A, Poerio V, Raimondi F, Mesuraca L, Crugliano C, et al. A comparison of nasal intermittent versus continuous positive air way pressure delivery for the treatment of moderate respiratory syndrome in preterm infants. *Minerva Pediatr*. 2007; 59: 91 – 95.
22. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Pediatric*. 2009; 98: 1412 – 1415.
23. Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: A randomized controlled trial. *Pediatrics*. 2011; 127(2): 300 – 307.
24. Louise S, Brett J. Nasal intermittent positive pressure ventilation in preterm infants: Equipment, evidence, and synchronization. *Seminars in Fatal & Neonatal Medicine*. 2016; 21: 146 – 153.
25. Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr*. 2005; 147(3): 341 – 347.
26. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. *Arch Dis Child Fetal Neonatal Ed*. doi:10.1136/adc.2010.205898.
27. Dargaville P A, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, et al. Continuous positive airway pressure failure in preterm infants: Incidence, predictors and consequences. *Neonatology*. 2013; 104: 8 – 14.
28. Pillai MS, Sankar MJ, Mani K, Agarwal R, Paul VK, Deorari AK. Clinical prediction score for nasal CPAP failure in pre-term VLBW neonates with early onset respiratory distress. *J Trop Pediatr*. 2011; 57: 274 – 279.
29. Manzar S, Nair AK, Pai MG, Paul J, Manikoth P, Georage M, et al. Use of nasal intermittent positive pressure ventilation to avoid intubation in neonates. *Saudi Med J*. 2004; 25: 1464 – 1467.
30. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(4): CD003063.
31. Aguilar S, Rodrigues T, Albuquerque M, Sampaio I, Cardoso B, Boto L, et al. Respiratory support strategy in 499 preterm newborns with gestational age ≤ 32 weeks. *Journal of Pediatric and Neonatal Individualized Medicine*. 2013; 2(1): 41 – 47.
32. Jobe A. Surfactant for respiratory distress syndrome. *Neoreviews*. 2014; 15: e236.
33. Polin RA, Waldemar A. Surfactant replacement therapy for preterm and term neonate with respiratory distress. *J Pediatrics*. 2013; doi: 10.1542/peds.2013-3443.